

Two Cases of Acute Febrile Neutrophilic Dermatitis Thought to be Caused by Topical Clindamycin

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Acute febrile neutrophilic dermatosis (AFND), or Sweet's syndrome, is characterized by the sudden onset of pyrexia, peripheral neutrophilia, and erythematous skin lesions, comprising massive neutrophilic infiltration in the dermis. Onset can be linked to various factors, including infection, inflammatory bowel disease (IBD), malignancy and medication. Drug-induced AFND (Di-AFND) is commonly associated with systemic administration of drugs. Clindamycin (CLD)-induced AFND has been documented in only a small number of cases (1, 2). Although topical CLD for acne has been used for many years, the frequencies of contact dermatitis and phototoxic reactions are low (3–7).

We report here 2 cases with unusual AFND, thought to be induced by CLD, with positive lymphocyte transformation test (LTT) or patch testing. Chemical peeling and light exposure might have led to the development of AFND in these patients.

CASE REPORTS

Case 1. A 23-year-old woman presented to our clinic with erythema, pustules and abscesses on the face and legs, together with high fever. Thirty-eight days prior to this first visit, she had started Clindamycin® Gel 1% (Kracie Pharmaceutical Ltd., Tokyo, Japan) just after a first chemical peeling procedure with 30% salicylic acid dissolved in macrogol for acne in an aesthetic dermatology clinic. Thirty-three days prior to her visit, chemical peeling was repeated. After the first treatment, intense pulsed light (IPL) (wavelengths 560–1,200 nm) was attempted instead of chemical peeling. She had been applying CLD until the day before her first visit despite the exacerbation. On examination, numerous pustules and abscesses with painful erythematous lesions were identified on her face (Fig. 1A), trunk and limbs where CLD had never been applied. No arthralgia or muscle pain was detected. Laboratory testing revealed elevations of both the white blood cell (WBC) count ($15.2 \times 10^3/\text{mm}^3$; 80.5% neutrophils) and the concentration of C-reactive protein (CRP) (7.3 mg/dl; normal, <0.03 mg/dl). Results of bacteriological cultures from an abscess on the neck and blood yielded negative results. Computed tomography showed no solid tumour or lymphoproliferative disorder. Skin biopsies from the neck and leg revealed neutrophilic pustules in the epidermis and a dense inflammatory infiltrate, mainly comprising neutrophils, throughout the entire dermis (Fig. 1B and Fig. S1¹). Leukocytoclastic vasculitis was absent. Based on these findings, a diagnosis of AFND or acne fulminans (AF) was suspected. Positive results were obtained from the LTT for CLD (stimulation index (SI) 10.28; positive ≥ 1.81) on her first visit, although patch testing for 10% petrolatum-based CLD had shown negative results. A diagnosis of CLD-induced AFND or AF was made. Oral predni-

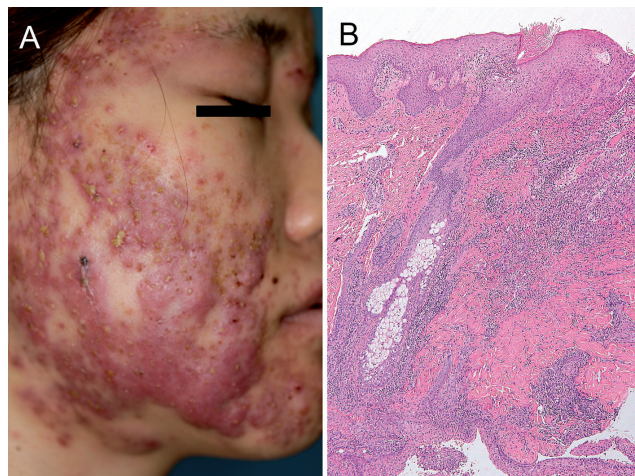


Fig. 1. Case 1. (A) Subcutaneous abscesses and pustules on the face with peri-orbital and nasal sparing. (B) Epidermal and dermal infiltration of inflammatory cells (haematoxylin-eosin (HE) stain; original magnification $\times 40$).

solone (PSL) was then started at 30 mg/day, and her symptoms promptly resolved.

Case 2. A 42-year-old woman presented with severe pustular eruptions and high fever. Four weeks prior to presentation, she had started oral PSL, 30 mg/day, for exacerbation of alopecia and facial erythema due to pre-existing systemic lupus erythematosus (SLE). Because she developed steroid-induced acne on the face, she had resumed using Dalacin® T Gel 1% (Sato Pharmaceutical Ltd, Tokyo, Japan). She had experienced no adverse effects with

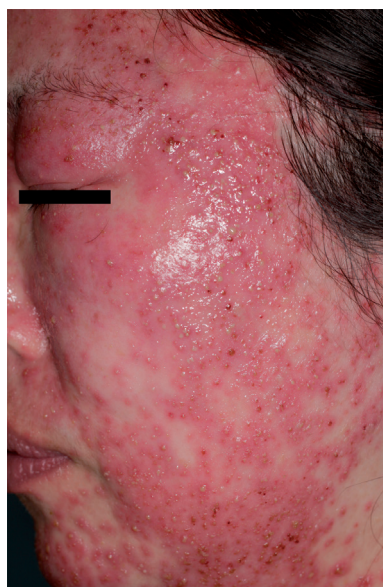


Fig. 2. Case 2. Erythema has coalesced into plaques studded with monomorphic pustules.

¹<https://doi.org/10.2340/00015555-3019>

use of CLD. Three days later, she noticed newly pruritic erythema over her entire face just after exposure to sunlight, and multiple non-follicular pustules then developed over the tender erythema (Fig. 2). On admission, these eruptions were also detected on the upper chest, where CLD had never been applied. Blood examination revealed elevations in both WBC count ($11.2 \times 10^3/\text{mm}^3$; 92.0% neutrophils) and CRP (1.5 mg/dl). No bacterial organisms were detected in blood and pustules. Extensive laboratory and radiographic work-up did not reveal any clear causative agent for her condition. Photosensitivity testing revealed hypersensitivity to ultraviolet (UV)-B (minimum erythema dose $4.5 \text{ mJ}/\text{cm}^2$). Skin biopsy revealed a subcorneal neutrophilic pustule with spongiosis in the epidermis and dense neutrophilic infiltration in the upper dermis, with no evidence of vasculitis (Fig. S2¹). After suspending application of CLD and preventing exposure to light, her symptoms improved. Patch testing with CLD at one week after admission yielded a positive result, but LTT for CLD performed 3 months after admission (at which time she was taking PSL, 10 mg/day) yielded a nearly positive result (SI 1.90). As a result, AFND or acute localized exanthematous pustulosis (ALEP) induced by CLD was suspected. PSL was tapered steadily from 30 mg/day to 5 mg/day without relapse.

DISCUSSION

Both of these cases showed acute onset of pustular erythematous eruptions, high-grade fever, elevations in neutrophil counts and inflammatory markers in the blood, and histopathologically dense neutrophilic infiltrations in the dermis. These clinical and laboratory features were compatible with a diagnosis of AFND, although case 1 was similar to AF and case 2 more closely resembled ALEP. No underlying malignant tumours, IBD or infections were detected and CLD was suspected of causing the symptoms from the positive result of LTT in case 1 and patch testing in case 2.

CLD has been reported in association with various adverse cutaneous reactions, including AFND (1, 2) and acute generalized exanthematous pustulosis (AGEP) (8–10)/ALEP (11). Clinical phenotypes in these 2 cases are atypical as AFND. However, Tam & Ingraffea also reported trimethoprim-sulfamethoxazole-induced Sweet's syndrome (SS), which displayed overlapping characteristics of SS and AGEP (12). Interestingly, neutrophilic eruptions in that case resulted from drug administration. Moreover, de Kort & de Groot reported CLD allergy presenting as rosacea (4) and Anavekar et al. reported facial SS mimicking AF (13). In terms of clinical features, their cases resembled case 1. Mecca et al. also reported a photo-distributed neutrophilic drug eruption (14), suggesting that AFND triggered by lights and drugs can be unusual. That case resembles case 2 in terms of clinical findings. Taken together, DiAFND seems to share similar characteristics with AF and AGEP/ALEP. In view of the drug-induced neutrophilic reaction detected, these disorders seem likely to exist in the same clinicopathological continuum.

Little information is available regarding CLD-induced AFND, although 2 cases have been documented (1, 2)

(Table S1¹). In the previously reported cases with CLD-induced AFND, clinical manifestations developed 2–3 days after initiating oral administration. In this regard, the interval between introduction of CLD and symptom onset in case 1 was quite different. Considering the long term before the drastic exacerbation in case 1, repeated chemical peeling and IPL exposure might have evoked abrupt and severe sensitization. On the other hand, several factors may have been involved in the development of AFND in case 2. This patient had previously applied topical CLD, and was exposed to excessive UV despite underlying photosensitivity. DiAFND was therefore considered likely to have developed in a shorter interval than case 1. Topical CLD sensitization may require a longer interval than systemic administration of CLD if no other susceptibility is present.

In conclusion, recognition that DiAFND may have similar characteristics to AGEP/ALEP and AF is important. DiAFND can be caused by topical CLD application under conditions associated with susceptibility, such as chemical peeling procedures and/or light exposure. Clinicians should be aware of this possibility.

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